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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,010	05/01/2001	Perry A. Frey	032026-0476D	5359

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,010	FREY ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,36-48 and 52-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,37-45 and 52-58* is/are rejected.

7)☒ Claim(s) *36 and 46-48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10[2005
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/13/2004 has been entered.

Applicants cancellation of claims 31-32 and 49-51 and the addition of claims 52-58, in the paper of 11/7/2005, are acknowledged. Claims 29, 30 and 36-48 and 52-58 are still at issue and are present for examination.

Applicants' arguments filed on 4/13/2004 and 11/7/2005, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 36, 46-48 are objected to because of the following informalities:

Claim 36 depends from rejected claim 29.

Claim 46 recites "(i) SEQ ID NO: 4-and (ii)". It is suggested this be amended to "(i) SEQ ID NO: 4 and (ii)"

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 30, 37-45 and 52-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was originally stated in the previous office action as it applied to previous claims 29, 30, 32, 37-45 and 49-51. In response to this rejection applicants have cancelled claims 31-32 and 49-51 and added new claims 52-58 and traverse this rejection as it applies to the remaining claims. Claims 52-58 are included in this rejection for the reasons previously stated for claims 29, 30, 32, 37-45 and 49-51 and those reasons stated below.

Applicants submit that the examiner has expressly acknowledged adequate written description for all the elements of the independent claims 29 and 30, with the exception of the genus of lysine 2,3-aminomutases employed in the claimed methods. Applicants submit that this argument is an insufficient basis to sustain the present written description rejection because proper genus analysis depends primarily on two factors: 1) whether the art indicates substantial variation among the species within the

genus of the claimed subject matter; and 2) whether a representative number of species is implicitly or explicitly disclosed in view of factor 1).

Applicants continue to traverse this rejection on the basis that applicants disclosure of eight previously unknown amino acid sequences for lysine 2,3-aminomutase enzymes provides a structure to function/activity relationship between the species that demonstrates applicants possession of all possible lysine 2,3-aminomutases. Applicants submit that the disclosure of these eight species readily reveal unique amino acid motifs that serve to identify all lysine 2,3-aminomutases. This argument continues to be acknowledged, however is found non-persuasive. Applicant's argument is found not persuasive on the basis that applicant's disclosure of eight species of the claimed genus is not sufficient to put applicants in possession of all enzymes having lysine 2,3-aminomutase activity, regardless of the source or structure of enzyme. Despite applicant's submission that applicants have identified a sufficient structure to function relationship between the disclosed species, no structure is used to describe the lysine 2,3-aminomutases used by the claimed methods. Thus applicants continue to claim methods of use of any lysine 2,3-aminomutases having any structure.

The mere contemplation of lysine 2,3-aminomutase from other species, as well as variants of such lysine 2,3-aminomutases and the use of such enzymes to prepare β-lysine, does not sufficiently describe the claimed genus of methods of use of any protein having lysine 2, 3-aminomutase activity. Applicants disclosure of the species of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, and 16 does not put applicants in possession of all possible

lysine 2,3-aminomutases and thus applicants were not in possession of the claimed methods of use of all possible lysine 2,3-aminomutases.

Applicants claims to more focused sub-genuses (i.e. claims 53, 57 and 58) while narrowing the claimed genus, continue to encompass inadequately described genuses with respect to the necessary lysine 2,3-aminomutases needed to practice the claimed methods. While the referred to claims narrow the claimed genus by the addition of source or limited structure, such is insufficient to adequately describe the claimed subgenus, based on the encompassed variability of those proteins having lysine 2,3-aminomutase activity and the number of species taught.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30, 38 and 39 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chirpich et al. I (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS).

As previously stated, Chirpich et al. I teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-β-lysine from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*).

Claims 30, 38 and 39 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chirpich et al. (Preparative Biochemistry. Vol. 3, No. 1, pp. 47-52, 1973, See PTO-892, ref U).

As previously stated, Chirpich et al. II teach the preparation of L-β-lysine from L-lysine comprising incubating L-lysine in a solution containing lysine 2,3-aminomutase from lysine-fermenting *clostridia* followed by the isolation/separation of L-β-lysine by differential elution. As the preparation yielded 123 millimoles or 61% based on the initial amount of lysine all cofactors required for lysine 2,3-aminomutase activity were present for the reaction.

Each of the above rejections rejection were originally stated in the previous office actions and repeated above for applicants convenience. Applicants have referred to the first Chirpich et al. reference used above as Chirpich et al. I and the second as Chirpich et al. II. Applicants appear to argue these rejections together. The reference to each of the two different Chirpich et al. references will be maintained as discussed below.

In response to these rejections applicants have not amended the claims but rather traverse the rejections as they apply to the claims. Applicants continue to submit

that applicants invention as defined by claim 30 distinguishes over both Chirpich et al. references by reciting a method of producing L-β-lysine, using a substantially pure lysine 2,3-aminomutase, as defined by applicants on page 4, lines 19-22, and that Chirpich et al. I does not teach a substantially pure lysine 2,3-aminomutase. Applicants assert that the enzyme activity isolated by Chirpich et al. I was not substantially pure lysine 2,3-aminomutase as defined by applicants disclosure. Applicants support this assertion by submission of a declaration by Frank Ruzicka (10/15/2003).

Applicants complete traversal is acknowledged and has been carefully considered, however, continues to be found non-persuasive for the reasons stated previously and repeated below.

Applicants traversal continues to be found not persuasive based on the following. Applicants specification states that **substantially pure** means that the desired purified protein is essentially free from contaminating cellular components, as evidenced by a single band following polyacrylamide-sodium dodecyl sulfate gel electrophoresis (SDS-PAGE). The term "substantially pure" is further meant to describe a molecule which is homogeneous by one or more purity or homogeneity characteristics used by those of skill in the art. The lysine 2,3-aminomutase taught by Chirpich et al. I was 95% homogeneous on the basis of disc gel electrophoresis and gel filtration, thus the lysine 2,3-aminomutase taught by Chirpich et al. I is encompassed by "a molecule which is homogeneous by one or more purity or homogeneity characteristics used by those of skill in the art" and thus "substantially pure".

In response to the above, applicants argue that one of skill in the art would readily understand that the above "non-denaturing gels" do not have the resolution of the SDS-PAGE gels used by applicants and cited in their definition of substantially pure and refer to the previously submitted affidavits and exhibits showing the superiority of applicants preparation. Applicants suggestion that this "evidence" is being ignored is noted, however, this is not found to be the case. The differences in applicants purified lysine 2,3-aminomutase and that taught by Chirpich et al. are acknowledged and appreciated, however, it remains that applicants claims continue to read on that taught by Chirpich et al. I. As stated previously and repeated above, applicants specification teaches that "The term 'substantially pure' is further meant to describe a molecule which is homogeneous by one or more purity or homogeneity characteristics used by those of skill in the art". It is further noted that applicants further list a number of such characteristics including molecular weight, chromatographic migration, amino acid composition, amino acid sequence, blocked or unblocked N-terminus, HPLC elution profile, biological activity and other such parameters.

It appears that much of applicants traversal is based on the differences in purity of applicants lysine 2,3-aminomutase and that taught by both Chirpich et al. refs. It appears that such a traversal is off mark, as the question is not one of "which preparation is more or less pure", but rather is the preparation taught by each of the Chirpich et al. refs encompassed by those preparations considered to be "substantially pure" by the skilled artisan. The examiner is of the opinion, as discussed above, that

each of the preparations taught by Chirpich et al are encompassed by the recitation "substantially pure".

Thus applicants traversal of each of the rejections over Chirpich et al. continues to not be found persuasive.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 37, 42, 43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chirpich et al. (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS).

This rejection was stated in the previous office action. As previously discussed, Chirpich et al. teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-β-lysine from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*). Chirpich et al. teach that their purification method is more effective than that which was previously reported.

One of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 to generate antibodies

against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for further use in the recombinant production and characterization of lysine 2,3-aminomutase. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al., which would involve the isolation of L-β-lysine from the cultured cells. The reasonable expectation of success comes from the high degree of knowledge in the art with respect to the isolation and recombinant expression of the genes which encode previously isolated proteins as well as the teachings of the isolation of the lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al. The reasonable expectation of success comes from the high degree of knowledge in the art with respect to the isolation and recombinant expression of the genes which encode previously isolated proteins as well as the teachings of the isolation of the lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al.

Applicants continue to traverse the rejection on the basis that the Examiner has not established a *prima facie* case of obviousness and submit that Chirpich et al. I does not teach a single element of applicants invention as defined by claim 29 (i.e.

prokaryotic host cell, expression vector, presence of L-lysine, expression by host cell and isolation of L-β-lysine, etc...). In response to this applicants are again reminded that this is an obviousness rejection, not a rejection based on anticipation. Applicants acknowledgement of such is recognized, as are applicants comments that the examiner is not relieved of the burden to show the basis for each and every element of the claims in the prior art. It is believed that the previous and current rejection addresses each of the limitations of the invention claimed, many of which are taught in the method or inherent to that method taught by Chirpich et al. I

Applicants continue to submit that the examiner has failed to show any suggestion or motivation to make the claimed invention, but rather has put forth an obvious to try rationale. Applicants argument is not found persuasive because as previously stated, Chirpich et al. teach the claimed method, with the exception of, using naturally produced lysine 2,3-aminomutase.

As previously stated, one of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for further use in the recombinant production and characterization of lysine 2,3-aminomutase. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a

protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al., which would involve the isolation of L-β-lysine from the cultured cells.

In response to applicants comments as to whether it is obvious to produce L-β-lysine by the claimed methods, as previously stated, any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al., which would involve the isolation of L-β-lysine from the cultured cells, making obvious the claimed methods.

Applicants continued comments regarding the purity of the preparation of Chirpich et al. have been addressed above under the 102 rejection, although applicants are reminded that this rejection is not based on anticipation, but rather obviousness and the production of a protein produced recombinantly would result in an increased purity of the produced protein relative to the naturally produced protein for the reasons previously discussed.

Applicants continued comments regarding the necessity of more then one protein for lysine 2,3-aminomutase activity are acknowledged, however not found persuasive on the basis that Chirpich et al. teach that the activity of lysine 2,3-aminomutase migrates and appears as a single peak/band in their experiments. The amount of time that has passed since the publication of Chirpich et al.'s articles and the present

application is acknowledged but not seen as relevant as to a measure of the motivation to make the claimed invention.

Claims 40 and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chirpich et al. (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS) as applied to claims 29, 37, 42, 43 and 45 above, further in view of Rozzell (U.S. Patent No. 4,88,0738), and Kusumoto et al. (Tetrahedron Letters, Vol 23, No. 29, pp 2961-2964).

The rejection was stated in the previous office action, and repeated below for applicants convenience.

As discussed previously, Chirpich et al. teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-□-lysine from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*). Chirpich et al. teach that their purification method is more effective than that which was previously reported.

Kusumoto et al. teach the synthesis of the antibiotic streptothricin F comprising adding β-lysine, carbamoyl and streptolidine moieties to the gulosamine molecule. Kusumoto et al. further teach that this synthesis method makes it possible to synthesize structural analogs of streptothricin which are necessary for the future studies of the relationship between structure and activity of the streptothricin antibiotic.

Rozzell teaches the biocatalytic methods for producing a desired amino acid using purified or partially purified enzymes either in solution or as immobilized enzymes.

One of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al., to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for use in the recombinant production lysine 2,3-aminomutase. One would have been further motivated to immobilize the recombinantly expressed lysine 2,3-aminomutase for use in a method of producing L-β lysine for use in the synthesis of the antibiotic streptothricin and streptothricin analogs, so that the enzyme could be used repeatedly in a process of synthesizing L-β-lysine. Further it is known in the art that enzyme immobilization is a means of stabilizing the enzyme and thus increasing the amount of L-β-lysine that is produced per lysine 2,3-aminomutase molecule/protein. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al. which would involve the isolation of L-β-lysine from the cultured cells. The reasonable expectation of success comes from the high degree of knowledge in the

art with respect to the isolation and recombinant expression of the genes which encode previously isolated proteins.

In response to this rejection, applicants continue to traverse as above that the cited art fails to teach the use of a substantially pure lysine 2,3-aminomutase. This is not found persuasive for each of the reasons discussed above, and as applicants have been reminded this is not a rejection based on anticipation, but rather on obviousness.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as previously stated, one of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al., to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for use in the recombinant production lysine 2,3-aminomutase.

One would have been further motivated to immobilize the recombinantly expressed lysine 2,3-aminomutase for use in a method of producing L-β lysine for use in the synthesis of the antibiotic streptothricin and streptothricin analogs, so that the

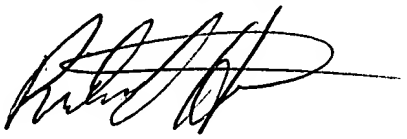
enzyme could be used repeatedly in a process of synthesizing L-β-lysine. Further, it is known in the art that enzyme immobilization is a means of stabilizing the enzyme and thus increasing the amount of L-β-lysine that is produced per lysine 2,3-aminomutase molecule/protein.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

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1/30/2006